

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 032174WOGP	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/HU2004/000073	International filing date (day/month/year) 08.07.2004	Priority date (day/month/year) 10.07.2003
International Patent Classification (IPC) or national classification and IPC C07C231/12, C07C231/24, C07C233/63		
Applicant RICHTER GEDEON VEGYESZETI GYAR RT.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 04.04.2005	Date of completion of this report 26.08.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Rufet, J Telephone No. +49 30 25901- 	

**INTERNATIONAL PRELIMINARY REPORT
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International application No.
PCT/HU2004/000073

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-11 as originally filed

Claims, Numbers

1-11 as originally filed

Drawings, Sheets

1-4 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3-11
	No: Claims	1-2
Inventive step (IS)	Yes: Claims	3-11
	No: Claims	1-2
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV.

The ISA found multiple inventions (3) in this application as follow:

invention I (claims 1-5, 11 partially):

Processes for the preparation of crystalline modification "G" or "H" of nateglinide according to the range of temperature of the acidic liberation

Invention II (claims 6-7):

Alternative process for the preparation of crystalline modification "H" of nateglinide by boiling another crystalline form in the presence of an alkane

Invention III (claims 8-10, 11 partially)

Alternative process for the preparation of chirally pure nateglinide wherein the acidic liberation is accomplished by adding the acid in two portions

The inventions listed above a priori do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature which defines the contribution of invention I over the prior art is, according to the applicant, the use of a specific range of temperature in carrying out the acidic liberation of the product in order to obtained crystalline modification forms of nateglinide namely "G" or "H". It is pointed out that this form "H" is already known from the prior art.

The special technical feature of invention II is the step of boiling another crystalline modification of nateglinide having lower melting points in the presence of an alkane in order to produce the known crystalline modification "H" of nateglinide.

The special technical feature of invention III is to carry out the acidic liberation of the product by adding the acid in two portions in order to obtain nateglinide in chirally pure form. It is stressed that this product is different to the products of the processes of inventions I and II. It is clear that the special technical features of inventions I, II and III are not so related as to form a single inventive concept.

Due to the fact that no other technical features can be regarded as special technical feature in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 3 inventions in the sense of rule 13.1 PCT.

The Applicant has paid extra fees, consequently the following opinion is based on the 3 inventions (subject-matter of claims 1-11).

Re Item V.

The following documents are referred to in this communication:

- D1 : J. MED. CHEM., vol. 32, 1989, p. 1436-1441, cited by Applicant
- D2 : EP-A-0196 222 corresponds to US-A-4816484 cited by Applicant
- D3: WO-A-03/093222
- D4: EP-A-1 334 963
- D5: WO-A-03/087038
- D6: WO-A-04/009532
- D7: US-A-5488150 cited by Applicant

It is pointed out that documents D3-D6 cited with the P category will not be considered in the present examination. It is expected that the claimed priority of the present application is valid (see EPO, J.O. 11/2001, p. 539-542, Point 13).

Novelty

I. Invention I (subject-matter of claims 1-5, 11 partially)

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 and 2 is not new in the sense of Article 33(2) PCT.

Documents D1 and D2 disclose also a process for the preparation of crystalline modification of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide) by treating the methyl ester according to formula (II) in methanol with a base (NaOH) followed by an acidic liberation at 20°C (or ambient temperature in D2).

It is stressed that an unclear expression such as "below room temperature" cannot be allowed in a claim if the expression is essential having regard to the invention. Equally, an unclear expression cannot be used by the applicant to distinguish his invention from the prior art.

2. The subject-matter of claims 3-5 and 11 (partially) appears to be novel over the prior art D1-D2, since the use of a temperature range of 65°C to 70°C during the acidic liberation step is not described in D1-D2.

II. Invention 2 (subject-matter of claims 6, 7)

1. None of the cited documents refers to a process for the preparation of Nateglinide in the crystalline form "H" from another crystalline modification form having a lower melting point than the form "H" by boiling in an alkane solvent.

D7 discloses also a recrystallisation process from the crystalline modification form "B" which has a lower melting point than the form "H" using as solvent water, acetone/water or alcohol/water mixtures (see example B1-B5).

The use of hexane as a possible "poor solvent" in combination with a "good solvent" is mentioned in D7, see column 4. However the use of hexane alone is not suggested.

The subject-matter of claims 6, 7 meets therefore the criteria of Article 33(2) PCT.

2. Starting from the closest prior art D7 the problem underlying this invention is to be seen in the provision of an alternative crystallisation process for the preparation of Nateglinide in the crystalline form "H". In view of example 3, it is credible that this problem has actually been solved by the technical measures of claim 6 in an unexpected way. It was not foreseeable for a skilled person, that the use of n-heptane instead of water, acetone/water or alcohol/water mixtures would allow to obtain the crystalline form "H" of Nateglinide in a short time (2 hours instead of overnight).

The subject-matter of claims 6, 7 meets therefore the criteria of Article 33(3) PCT.

III. Invention 3 (subject-matter of claims 8-10 and 11 partially)

1. None of the cited documents refers to a process for the preparation of chirally pure Nateglinide from the alkali salt, wherein the acidic liberation of the product is accomplished by adding the acid in 2 portions in such a way that the first time less than equimolar amount of the acid is added. The subject-matter of invention 3 meets therefore the criteria of Article 33(2) PCT.

2. Starting from the equally closest prior art D1, D2 or D7, the problem underlying this invention is to be seen in the provision of an alternative process for the preparation of chirally pure Nateglinide (i.e. no enantiomeric impurity; see p. 4, I. 3).

In view of example 4, it is credible that this problem has actually been solved by the technical measures of claims 8-11 in an unexpected way, since it was not foreseeable for a skilled person that chirally pure Nateglinide could be obtained without adding any chiral reagent.

The subject-matter of invention 3 meets therefore the criteria of Article 33(3) PCT.

Re Item VIII.

1. According to page 3, paragraph 4, the presence of a water-miscible organic solvent is an essential measure of the process of invention 1 and should therefore be present in the main claim.
2. Claims 2 and 9 appear not to be supported by the description as far as the expression "aqueous methanol.....is employed" is concerned.
3. The expression "room temperature" used in claims 1 and 3 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear.
4. The expression "lower melting point" used in claim 6 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear.
5. The use of the expression "preferably" or "more preferably" in claims 1-4, 6 and 9 renders the subject-matter of those claims unclear since it introduces an ambiguity in the claims. It is stressed that these expressions have no limiting effect on the scope of the claims. The feature following these expressions is to be regarded as entirely optional.